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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,398	08/03/2000	ABDESSATAR CHTOUROU	065691/0193	9759

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EXAMINER
MOHAMED, ABDEL A

ART UNIT	PAPER NUMBER
1653	6

DATE MAILED: 12/18/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/581,398	Applicant(s) CHTOUROU ET AL.	
	Examiner Abdel A. Mohamed	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 August 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

ACKNOWLEDGMENT FOR PRIORITY, IDS, STATUS OF THE APPLICATION AND THE CLAIMS

1. This application is filed under 35 U.S.C. 371 on 8/3/00 having a filing date of 12/14/98 of PCT/FR98/02715. Acknowledgment is made of Applicant's claim for priority based on French application number 97 15888 having a filing date of 12/15/97. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119, which papers have been placed of record in the file. The Information Disclosure Statement (IDS) and Form PTO-1449 filed 11/1/00 are acknowledged, entered and considered. Claims 1-23 are present for examination.

2. The specification is objected because there are no Headings disclosed in the disclosure and the following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the Applicant's use.

ARRANGEMENT OF THE SPECIFICATION

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.

(b) Cross-References to Related Applications.

(c) Statement Regarding Federally Sponsored Research or Development.

(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).

(e) Background of the Invention.

1. Field of the Invention.

2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) Brief Summary of the Invention.

(g) Brief Description of the Several Views of the Drawing(s).

(h) Detailed Description of the Invention.

(I) Claim or Claims (commencing on a separate sheet).

(j) Abstract of the Disclosure (commencing on a separate sheet).

(k) Drawings.

(l) Sequence Listing (see 37 CFR 1.821-1.825).

TITLE OF THE INVENTION

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

ABSTRACT MISSING

4. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

OBJECTIONS TO TRADEMARKS AND THEIR USE

5. The use of trademark "Planova®" has been noted in this application. The trademark has not been capitalized, it should be capitalized whenever it appears and be accompanied by the generic terminology. Although, the use of trademark is permissible in patent applications, the proprietary nature of the mark should be respected and every effort made to prevent its use in a manner which might adversely affect their validity as trademark.

Further, the specification which specifies the generic terminology should include published product information sufficient to show that the generic terminology or the generic description is inherent in the article referred by the trademark. This description requirement is made because the nature and composition of articles denoted by trademark can change and affect the adequacy of the disclosure.

IMPROPER MULTIPLE DEPENDENT CLAIMS

6. Claims 6-23 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only and/or cannot depend from any other multiple dependent claims. See MPEP § 608.01(n). However, the claims have been treated on the merits as soley dependent upon method of preparing virus free FVIII solution by filtration.

CLAIM REJECTION-35 U.S.C. § 112, FIRST PARAGRAPH

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Dissociation step(s) is/are critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). Claim 1 recites a solution containing highly or very highly pure FVIII is prepared....., however, the claim does not recite the essential step(s) of dissociation of high molecular weight FVIII-vWF complex for the preparation of a solution containing high or very highly pure FVIII.

CLAIMS ARE A LITERAL TRANSLATION

8. The claims are generally narrative and indefinite and fail to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

CLAIMS REJECTION-35 U.S.C. § 112 2nd PARAGRAPH

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claim 1 is indefinite and confusing because the preamble of the claim is not commensurate with the body of the claim. That is, the preamble recites method for preparing, by filtration, a factor VIII solution.....while the body of the claim is devoid of any positive method except for recitation a step is carried out, of filtration of said solution. Thus, the body of the claim recites a solution containing highly or very highly pure factor VIII is prepared, which is essentially devoid of high molecular weight factor VIII-vWF complexes. Therefore, it is not clear how the intended/desired method of preparing by filtration a viral free FVIII solution is/are achieved. Further, the claims is incomplete in failing to recite method step(s) for preparing by filtration of FVIII solution. Although, claim 1 states "filtration.....", but, the claim does not use active method step(s) i.e., filtering.....ect., and it is not clear how the step(s) of filtration alone would result in obtaining/preparing a solution containing highly or very highly pure FVIII, which is essentially devoid of high molecular weight FVIII-vWF complexes and is free of virus. Appropriate clarification is required.

The terms "high molecular weight", "high or very high purity", "as low as", "essentially", "sufficient amount", "lower than", "at least equal to" and "approximately" in claims 1, 2, 3, and 18-20, respectively are relative terms which render the claims indefinite. The terms "high molecular weight", "high or very high purity", "as low as", "essentially", "sufficient amount",

"lower than", "at least equal to" and "approximately" are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention because the above terms are relative expressions and as such it is not clear nor ascertainable whether the expression does provide a degree of leeway with respect to range.

Claims 1 and 2 are indefinite in the recitation the acronym "vWF". Use of the full terminology at least in the first occurrence would obviate this rejection.

Claims 2-20 are indefinite in the recitation "characterized in that" because the characterization of use can recited by amending the claims to recite "wherein" or "comprising", etc. Thus, it is suggested that the term "wherein" or "comprising", etc. be replaced in the recitation thereof.

Claims 2 and 3 recite the limitation "the dissociation" and "said dissociation step", in lines 2 and 3, respectively. There is insufficient antecedent basis for this limitation in claim 1 or claim 2 or claim 3, respectively.

Claims 6 and 8 are indefinite in the recitation "from 0.2 M to salt saturation" and "0.35 M to saturation", respectively because it is not clear at what M the saturation occurs. Amendment of the claims to recite a definite saturation point is suggested.

Claim 7 is indefinite in the recitation "said solution" because it is not clear if the claim is referring to saline solution or to FVIII solution. Appropriate clarification is required.

Claims 9 and 11 are indefinite and confusing in the recitation "step b)" because there is no step b) recited in claim 1 or in any of the preceding claims.

Claim 9 is also indefinite and confusing in the recitation "step b) is carried out at a pressure lower than the recommendation threshold recommended by the supplier" because it is not disclosed and/or defined in the claim or in the specification the threshold recommended by the supplier. Appropriate clarification is required.

Claim 10 contains the trademark/trade name Planova®. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a filter membrane and, accordingly, the identification/description is indefinite.

Claims 10 and 18 are indefinite and vague in the recitation ".....0.3 bar, preferably.....0.2 bar" (claim 10) and ".....50 IU/mg, preferably.....100 IU/mg" (claim 18), respectively because the claims recite two different ranges in one claim, respectively. If Applicant intends to claim the preferred ranges as well as the broad ranges, then, the Office recommends the use of two dependent claims claiming the recited ranges, respectively.

Similarly, claims 19 and 20 are indefinite and vague in the recitation "....from approximately 2 to approximately 100 U/ml, preferably from approximately 10 to approximately 50 U/ml" (claim 19) and "...from approximately 0.05 to approximately 0.5 mg/ml, preferably from approximately 0.1 to approximately 0.5 mg/ml" (claim 20), respectively for the same reasons discussed under the rejection of claims 10 and 18 and 1-3 and 18-20 above.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 12 recites the broad recitation by purification of a plasmatic fraction, and the claim also recites purification of cryoprecipitate fraction of the plasma by ion exchange chromatography which is the narrower statement of the range/limitation.

Claim 13 recites the limitation "the dissociating conditions of step a)" in lines 4-5. There is insufficient antecedent basis for this limitation in claim 1 or 13 or in any of the preceding claims.

Claims 12 and 14-20 are indefinite in the recitation "the starting FVIII solution". It appears that there is no proper antecedent for the above phrase in claims 1 or in each of the claims recited above.

Claim 13 recites the limitation "the concentrated FVIII fraction" in line 2. There is insufficient antecedent basis for this limitation in claim 1 or 13 or in any of the preceding claims.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 14 recites the broad recitation by purification of a plasmatic fraction, and the claim also recites purification of cryoprecipitated fraction of the plasma by heparin precipitation which is the narrower statement of the range/limitation.

Claim 15 is indefinite in the recitation "inactivated by solvent/detergent treatment" because it contains the use of an alternative expression wherein the limitation covers two elements, i.e., "solvent" is not the same as "detergent" and vise versa.

Claim 20 recites the limitation "the protein content" in line 2. There is insufficient antecedent basis for this limitation in claim 1 or claim 20 or in any of the preceding claims.

CLAIMS REJECTION-35 U.S.C. § 103(a)

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/00237 taken with Josic et al. (J. Chromatogr. B. Biomed. Appl., Vol. 662, No. 2, pp. 181-190, 1994), Grandgeorge et al (U.S. Patent No. 5,371,195) and Farb et al (U.S. Patent No. 4,758,657).

WO 96/00237 teaches a method of virus-filtering a solution that contains at least one macromolecule, particularly factor VIII which may be native or recombinant, wherein the salt content of the solution lies in the range of from about 0.2 M up to saturation of the solution with the salt concerned (See e.g., abstract, page 5, lines 14 to 24 and claim 1). On page 7, lines 30 to page 9, lines 27, the reference clearly teaches the use of various filters which are readily available commercially such as Planova™ 15 filter for virus filtration having a porosity as low as 15 nm for the intended purpose of reducing the content of very small non-enveloped viruses, such as parvoviruse, polio virus, hepatitis virus, ect. Thus, the primary reference clearly teaches a method for obtaining a variety of safe solution of the plasma protein complex such as FVIII by a filtration step using a filter with a porosity of 15 nm.

The primary reference of WO 96/00237 differs from claims 1-23 in not using chaotropic ions such as calcium for dissociation purpose and the purification of the cryoprecipitate fraction of the plasma by ion exchange chromatography. However, Josic et al. teach the purification of FVIII and vWF from human plasma by anion-exchange chromatography, wherein the purification is carried out by a combination of precipitation and chromatographic procedures. After precipitation, the first step in virus inactivation is achieved through the effect of a non-ionic

detergent such as Tween 80, and as solvent such as TnBp (i.e., inactivated by solvent/detergent treatment as claimed in claim 15). By anion-exchange chromatography, a highly enriched product consisting of a complex formed by FVIII and vWF is isolated. The second step in virus inactivation is conducted with the addition of stabilizers, pasteurization and subsequent removal by ion-exchange chromatography. The resulting complex of FVIII and vWF are dissociated by adding calcium ions and subsequently both glycoproteins from the complex are separated from one another by further anion-exchange chromatography (See e.g. abstract, pages 183-184 and Figure 1). Thus, clearly teaching the separation of FVIII and vWF using treatment by calcium ions after purification of the FVIII-vWF plasma complex using chromatographic techniques.

Further, Grandgeorge et al (U.S. Patent No. 5,71,195) teaches a method for purifying FVIII from cryoprecipitate, enabling chromatographic yields of more than 90% to be achieved by dissolving FVIII and subjecting to viral inactivation with solvent/detergent and further subjecting to chromatography on a weak anion-exchange column which is hydrophilic in nature and FVIII is then eluted with a dissociating buffer (See e.g. abstract and summary of the invention). Furthermore, Farb et al discloses a multi-step process for separating FVIII from plasma in which at least one of the steps require the adsorption of FVIII on a hydrophilic interaction matrix (See e.g. summary of the invention). Moreover, as acknowledged on page 2, lines 23-32 in the instant specification, the elimination of vWF proteins (that is, implicitly, high molecular weight vWF, and therefore, implicitly, free of high molecular weight vWF). Thus in view of this and in view of the teachings of the secondary references, one of ordinary skill in the art could have envisaged

filtering the solution of dissociated FVIII/vWF which is obtained as a product which is free of virus and devoid of vWF by combining a filtration and dissociation steps using a filter with a porosity of 15 nm. Therefore, it would have been obvious to one of ordinary skill in the art to apply the teachings of the secondary references to the primary reference because such features are known or suggested in the art, as seen in the secondary references, and including such features into the methods of the primary reference would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof.

With respect to claim 21-23, the claims are in product-by-process format and as such, it is the novelty and patentability of the instantly claimed product that need be established and not the recited process steps, In re Brown, 173 USPQ 685 (CCPA 1972); In re Wertheim, 191 USPQ (CCPA 1976). Further, the prior art described the product as old, In re Best, 195 USPQ 430, 433 (CCPA 1977); (See MPEP 706.03 [e]). Hence, the burden of proving that the process limitation makes a different product is shifted to the Applicants, In re Fitzgerald, 205 USPQ 594.

Therefore, in view of the above and in view of the combined teachings of the prior art, one of ordinary skill in the art would have been motivated to employ a method for obtaining a virus free solution of the plasma protein complex of FVIII, said solution essentially being free of high molecular weight vWF and obtained from a solution containing high molecular weight FVIII-vWF complexes, said method combining a dissociation step and a filtration step using a filter with a porosity of 15 nm., absence of sufficient objective factual evidence or unexpected results to the contrary.

CITATION OF RELEVANT PRIOR ART

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

WO 98/37086 discloses methods for recovering viruses from protein solution by nanofiltration through a membrane with an average size of 15 nm (i.e. Planova 15 N).

Zou et al (U.S. Patent No. 5,677,162) describe a method for activating prothrombin to thrombin in a prothrombin complex composition without using exogenous animal components such as snake venom and thromboplastin by controlling various conditions such as pH, temperature, calcium concentration and viral removal by 15 nanometer filtration (i.e., using PLANOVA® 15N).

CONCLUSION AND FUTURE CORRESPONDENCE

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m.. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (703) 308-2923. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Christopher S. F. Low

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